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Renal function in general as well as many essential body functions and systemic parameters undergo pronounced circadian fluctuations [8]. Among these systems is mineral homeostasis where the concentration of calcium and phosphate in blood and hormones such as Parathyroid hormone (PTH), Fibroblast Growth Factor 23 (FGF23), and α-Klotho regulate mineral balance.

Chronic kidney disease (CKD) is a devastating disease affecting mineral balance and leading eventually to phosphate overload with excessively increased morbidity and mortality due to cardiovascular disease (CVD) [13,14]. Elevated PTH, FGF23 and phosphate have been independently associated with cardiovascular disease in CKD and at least in the case of phosphate, evidence from experimental animal models and clinical studies is overwhelming to demonstrate a direct causal link between phosphate and mechanisms leading to CVD.

Disordered mineral balance in kidney disease starts very early. During acute kidney injury (AKI) FGF23 rises rapidly and massively [6,2]. Similar in CKD, FGF23 rises very early and slowly when glomerular filtration rate (GFR) declines [11,9,4]. Also α-Klotho levels in kidney, circulation and urine fall and this may even precede the rise in FGF23. Also levels of calcitriol decrease progressively. Later in the progress of CKD, PTH increases and only in late stages also serum phosphate is elevated. At the same time, loss of circadian rhythms for plasma phosphate, calcium, PTH and FGF23 ensues.

Neutralization of FGF23 with neutralizing antibodies has shown that FGF23 plays an important role in early kidney disease to protect against phosphate overload and CVD [12]. However, it has remained unclear what triggers the early rise of FGF23 as plasma phosphate levels tend to be rather low in early CKD. FGF23 is enzymatically degraded probably involving sortilin-like proteases, it may in part be cleared by renal excretion and both processes appear to be reduced in kidney disease. Moreover, we and others found that proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin 1β (Il-1β) and Il-6 stimulate FGF23 production [7,5,3].

In this issue of Pflügers Archiv, Nordholm and colleagues add another facet to this puzzling picture [10]. They analyze the circadian fluctuations of various circulating parameters of mineral homeostasis together with activin A in normal rats and rats with reduced kidney function consuming different diets with increasing phosphate content. Their results not only confirm the loss or changes in circadian rhythmicity of important players in mineral homeostasis but they show that activin A levels are increased in animals with reduced kidney function, further increased by high phosphate intake, and that the circadian rhythm of activin A shows a reduced amplitude in CKD models.

Why could this be of interest ?

Activin A is a glycoprotein that either alone or after forming heterodimers together with activin B acts as endocrine factor. Initially recognized as a positive regulator for follicle-stimulating hormone (FSH) release, it has become clear that particularly activin A plays many more roles in normal physiology and disease processes (for review see: [1]). Activin A belongs to the superfamily of transforming growth factor β (TGF-β) and is signaling through ActRIIA/B receptors and Smads to alter transcription of target genes. Activin A and its receptors are widely expressed in many tissues including

kidney where it is involved in branching morphogenesis and kidney repair, in brain where it has neuron-protective functions, and in heart and the vascular system where it controls cardiac myogenesis and cardiac remodeling.

In kidney, activin A is produced by peritubular myofibroblasts activated during kidney disease and repair processes. It suppresses renal α-Klotho levels which may be of importance as α-Klotho is required for canonical FGF23 signaling and has been shown to exert protective effects on kidney and cardiovascular structures and functions. Activin A stimulates proliferation of fibroblasts and induces fibrosis at the same time inhibiting tubular cell proliferation and differentiation.

Additional effects of activin A on skeletal muscle and bone may be important for our understanding of the mineral-bone-disorder in CKD patients (CKD-MBD). Activin A has negative effects on skeletal muscle recovery and proliferation. The effects of activin A on adult bone are controversial and activin A may have stimulatory effects on osteoblasts and bone mineralization as well as induce osteoclasts and reduce bone mineralization. Obviously, these processes are disturbed in CKD-MBD and whether activin A signaling may contribute remains to be clarified. Some of the controversial effects may be explained by altered circadian rhythms of hormones like PTH or activin A and the results reported by Nordholm and colleagues may promote further research in this direction.

The recognition of activin A as an additional factor produced by the injured kidney and acting on target organs involved in the pathogenesis of CKD-MBD makes this an interesting molecule not only for our understanding of the disease but also as a potential marker of disease progression or even as a novel target for interventions.

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